REMARKS

Status of the Claims

Claims 9, 15, 16, 34 and 40-48 are pending in the application. Claims 9, 15, 16, 34 and 40-48 have been rejected. Previous rejections of the claims under 35 U.S.C. § 112, first paragraph and for double patenting have been withdrawn. Claim 9 has been amended to recite that the route of administration is limited to intramuscular administration, and claim 40 has been amended to recite that the DNA is "free" DNA. Support for these amendments can be found throughout the application, for example, Example 1 and the as-filed claims. Claims 34 and 47 have been canceled. The claims remain rejected under 35 U.S.C. § 103 for allegedly being obvious. Upon entry of this amendment Claims 9, 15, 16, 40-46, and 48 will be pending. No new matter has been amended.

Rejection Under 35 U.S.C. 103

Claims 9, 15, 16, 34 and 40-48 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent Application Publication No. 2004/0063652 to Jolly; Kataoaka et al, J. Biol. Chem 272(29):18209-15; U.S. Patent No. 5,783,567 to Hedley et al.; Samlowski et al (1988) Regional Immunology 1(1): 41-55; and U.S. Patent No. 5,763,416 to Bonadio et al.

According to the Office, the combination of the prior art yields the present invention. Jolly is alleged to discuss the use plasmids to transform macrophages, to effect killing and for general secretion of proteins that block pathogenic interactions local to the cell. Kataoka is alleged to discuss the human CD156 gene and its promoter sequence as specific for macrophage expression, as well as the structure of such promoters. Hedley is alleged to discuss the transformation of macrophages in the draining lymph nodes by subcutaneous injection of DNA. Samlowski is alleged to discuss that macrophages were known to drain to the lymph nodes local to the site of injection. Bonadio is alleged to teach that the SV40 polyA signal is a standard signal for termination of transcripts. Additionally, the Office alleges that one of skill in the art

knew to numb an injection site when injecting substances, and that bupivacaine is a well known numbing agent.

The Office alleges that the invention would have been obvious because "in essence Applicant's claim reflect what is already known in the Art to occur and is simply another method that the Artisan would be capable of performing prior to the invention in order to get proteins into the lymph nodes." (Office Action, page 5). The Office alleges that "the Art demonstrates that the methods of transforming macrophages, the use of promoters specific for macrophages to effect their tissue-specific expression in macrophages, the use of secretion signals, and the use of the polyA tails was well known in the art. "Still further, and critically, the Art recognized that macrophages drained into lymph nodes local to their tissue site, as shown in Samlowski." (Office Action, page 6) The Office alleges that whether the claims are obvious comes down to "whether or not the Artisan would have been able to put together these functions and utilize them [to] derive a method encompassed by the claims." (Office Action, page 6). The Office alleges that the claims are obvious because the "knowledge is within the skill of the Artisan, and the non-specific motivation is the combined knowledge in the Art that the macrophages drain to the local lymph nodes, with the known mechanisms of causing the macrophages to secrete a protein. Applicants respectfully disagree.

The claimed invention is not obvious. The cited art has not been interpreted accurately by the Office. Proper consideration of the art does not establish a prima facie case of obviousness. Moreover, there is nothing within the amorphous "combined knowledge" that would have led to the combination of the claimed invention. Finally, those skilled in the art viewing the art would not recognize the benefits achieved by the claimed invention.

The pending claims are not obvious because the cited references do not yield the present invention, teach away from the pending claims, and even if the references are combined to yield the present invention do not give rise to a reasonable expectation of success. Claim 9 has been amended to recite the route of administration is intramuscular. Claim 40 has been amended to recite that the DNA molecule is a free DNA molecule. Free DNA molecule is referred to in Example 1 of the present application. Example 1 refers to the injection of a composition

comprising bupivacaine and DNA and reflects that the DNA is not incorporated into particles or viral vectors.

None of the references discuss the step of identifying a lymphnode as a target for delivery of a protein and locating a site that is proximal to the lymphnode. None of the references disclose that upon administration of the DNA to an individual, the DNA is taken up by the macrophage cell and the macrophage then drains to the lymphnode.

The Jolly references discloses expressing a protein in a macrophage by introducing a vector that comprises the protein's nucleic acid coding sequence under the control of a macrophage specific promoter into a macrophage. Jolly, however, does not disclose how to administer the vector to the macrophage. Additionally, the Jolly reference fails to disclose the step of identifying a lymph node and the delivery of a protein to the lymph node by administering DNA to a site located on the individual's body that is proximal to the lymphnode.

The remaining references to do not make up the deficiencies of Jolly.

The Hedley reference teaches away from the use of free DNA and intramuscular administration. The Hedley references discusses microparticles that are effective for delivering DNA to be taken up by phagocytic cells.

With reference to macrophages, the Hedley reference expressly teaches away from using intramuscular injection. The Hedley reference discloses a specific method for delivering DNA that is encapsulated in microparticles to cells in the lymph node, stating: "one can target, via ***subcutaneous injection***, take up by the phagocytic cells of the draining lymph nodes." (Col. 8, lines 22-24, emphasis added). A careful reading of the Hedley reference reveals that the microparticles comprising DNA are injected subcutaneously and are taken up by cells in the lymph nodes. The Hedley reference teaches intramuscular administration of microparticles comprising DNA to target dendritic cells in the skin. *Id.* The Hedley reference does not teach intramuscular administration for delivery to macrophage cells which migrate to the lymph node. Rather, one skilled in the art reading the Hedley reference would conclude that subcutaneous delivery of microparticles is required to deliver the DNA to macrophage in the lymph nodes.

In addition to teaching away from using intramuscular injection, the Hedley reference also teaches away from using free DNA. The Hedley reference in its examples emphasizes the effectiveness of using microparticles to deliver DNA and how it is superior to using other forms of DNA including naked DNA. The Hedley references teaches one of skill in the art to use microparticles to deliver a DNA molecule instead of using naked DNA (see, for example, Hedley, Col. 18, lines 35-49). One of skill in the art, considering the Hedley reference in its entirety, would use microparticles as opposed to free DNA because of the Hedley reference teaches the relative ineffectiveness of using free DNA.

One skilled in the art would not combine the Hedley reference with the combination of Jolly; Kataoaka et al, Samlowski et al and Bonadio et al. As noted above, Jolly does not disclose elements of the claims and the combination of Kataoaka et al, Samlowski et al and Bonadio et al. do not make up for the deficiencies in Jolly. Thus, there is no prima facie case of obviousness.

In addition, if one skilled in the art combined the teachings of Hedley with Jolly, Kataoaka et al, Samlowski et al and Bonadio et al., the benefits of the invention would not be expected. One of skill in the art would not have expected that intramuscular injection would result in delivery a protein to a lymph node nor would they expect that free DNA could be used to deliver a protein to a lymph node.

None of the references cited indicate that intramuscular injection of DNA would result in the delivery of DNA to macrophage which would then migrate to the lymph nodes. The combination of references simply does not provide any indication that such a result would be expected.

Likewise, the combination of references does not provide any indication that free DNA could be used to deliver DNA to macrophage which then migrate to the lymph nodes. The present specification states, "surprisingly the [free] DNA is not degraded in this process." (Specification, page 39, lines 5-6).

As discussed above, the Jolly reference only refers to delivering a DNA molecule to a macrophage but does not teach how to do this. The Hedley reference specifies delivering DNA

by using microparticles and that delivery of the microparticles to cells in the lymph nodes is achieved via subcutaneous injection. The other art cited by the Office does not give rise to an expectation of success for one of skill in the art. Therefore, based upon the cited prior art it would have been unexpected that one of skill in the art could have.

Prior to the present invention it was not known or obvious that one could deliver a protein to a lymphnode by the method described in the pending claims. Here, applicants have shown that DNA injected intramuscularly is taken up by macrophage which then travel to the lymph node, whereupon the DNA is expressed to effectively deliver the protein to the lymph node. Applicants have shown that free DNA directly injected into an individual remains intact and functional such that when taken up by macrophage which travel to the lymph node, the DNA can be expressed to effectively deliver the protein to the lymph node. Those skilled in the art would not have expected these beneficial aspects in view of the combination of references.

In anticipation of an appeal, the Office generally argues that because the methods described in Jolly and Hedley and the knowledge of Samlowski was known that one of skill in the art could have derived the present invention. However, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some ***articulated reasoning*** with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 127 S. Ct. 1727, 1741 (2007). The Office has not put forward any articulated reasoning with some rational underpinning to support its legal conclusion of obviousness. The Office's only claim is that there are references that discuss macrophage specific expression and that microparticles can be taken up by macrophages via subcutaneous injection . The Office, however, has failed to articulate a reason why one of skill in the art would have extrapolated any of these methods to those to derive what is now claimed. Therefore, the claims are nonobvious because the Office has failed to articulate a reason with some rational underpinning to support its legal conclusion of obviousness for the reasons stated above.

In view of the foregoing, Applicants request the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Claims 9, 15, 16, and 40-46, and 48 are in condition for allowance. A notice of allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully Submitted,

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